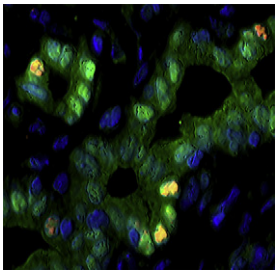
In This Issue

Cell

Adult Progenitors for Pancreas Regeneration



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Whether progenitors for pancreatic β cells exist in adult mammals has been a question of controversy in diabetes research. Xu et al. have now isolated a cell type from injured pancreases of adult mice, which is similar to the islet cell progenitor in embryonic pancreas. This adult multipotent progenitor cell can be activated cell autonomously to give rise to all islet cell types, including glucose-responsive beta cells that can subsequently proliferate. The findings suggest new therapeutic avenues for diabetes treatment.

A Transposase with a Hybrid under the Hood

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Different DNA transposition systems move DNA segments from one genomic location to another using a variety of distinct mechanisms. Through structural investigation of IS608, an insertion sequence from Helicobacter pylori, Barabas et al. report a surprising mechanism involving large-scale conformational changes in the self-encoded transposase enzyme, which acts on only one strand of the transposon. A crucial feature is that the transposase co-opts single-stranded transposon DNA to be part of its active site and, through base pairing interactions, uses it to recognize its cleavage and integration sites. Thus, this transposon solves the problem of site-specific DNA recognition with a hybrid active site.

Keeping Transcription in *Chk* after DNA Damage

PAGE 221

DNA damage triggers multiple cellular responses, including changes in gene expression. Whereas DNA damage-induced transcriptional activation has been well characterized, mechanisms of transcriptional suppression are largely unexplored. The kinase Chk1 is an important mediator of the DNA-damage response and is known to dissociate from chromatin after DNA damage. Shimada et al. now find that this dissociation results in a decrease of histone H3 phosphorylation and find that Chk1 directly phosphorylates histone H3-T11. Reduced H3-T11 phosphorylation causes decreased gene expression of cell-cycle regulators, contributing to the DNA-damage cell-cycle arrest. These results suggest a mechanism by which Chk1 acts as a histone kinase responsible for DNA damage-induced transcriptional repression.

Mitotic Checkpoint Protein Gets a Fix on Chromosome Attachment Errors

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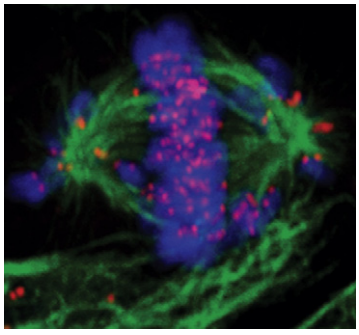

Maintenance of chromosomal stability relies on coordination between various processes that are critical for proper chromosome segregation in mitosis. These processes include correction of erroneous attachments of kinetochores to spindle microtubules and the mitotic checkpoint response to such attachments that halts cell-cycle progression until correction is achieved. Jelluma et al. now identify the Mps1 kinase, previously implicated in the mitotic checkpoint, as a regulator of the chromosomal passenger complex that is responsible for error correction and show that the Aurora B-regulatory protein Borealin is a functional substrate for Mps1 in this control. Mps1 thus coordinates two crucial responses to unproductive chromosome attachments.

Sugar-Coating Notch Signaling

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Protein O-glucosylation is a posttranslational modification that occurs in the EGF repeats of a few proteins, including coagulation factor VII and IX and Notch. However, the gene(s) encoding the O-glucosyltransferase have eluded identification. Here, Acar et al. show that a *Drosophila* gene termed *Rumi* encodes an endoplasmic reticulum protein that glucosylates Notch. Loss of this enzyme causes a temperature-sensitive misfolding of Notch. Although this misfolded Notch traffics to the cell membrane where it interacts with its extracellular ligands, it fails to be cleaved by extracellular proteases that normally cleave Notch, thereby causing a failure in Notch signaling. Thus, the authors have uncovered the function for O-glucose modification of Notch in vivo and identified the O-glucosyltransferase.

Navigating IL-4 Receptor Signaling

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The cytokines IL-4 and IL-13 play critical roles in allergy and asthma by binding to different combinations of shared receptors. LaPorte et al. determined the three-dimensional structures of three cytokine-receptor complexes that comprise the IL-4/IL-13 system. These findings define the molecular basis of receptor and ligand "sharing" and revealed unexpectedly different assembly properties of the signaling complexes on cell surfaces that could impact function. Collectively, these studies show that extracellular receptor-ligand interactions are not simply "on/off" switches for signal transduction, but may instigate divergent signaling responses through shared receptors, which could be utilized in developing therapeutic agents targeting this receptor system.

A New Horse in the Photosynthesis Carousel

PAGE 273

To adjust photosynthesis in response to environmental and cellular demands plants are capable of switching between linear and cyclic electron flow. Cyclic electron flow generates ATP and involves the photosystem I, but with the exception of one protein, PGR5, other components facilitating cyclic electron flow are unknown. DalCorso et al. show that the PGRL1 protein interacts functionally and physically with PGR5 and other photosynthetic proteins including photosystem I. The authors propose that a PGRL1-containing complex may facilitate cyclic electron flow around photosystem I.

Rab and Arf Tag-Team in Membrane Attachment

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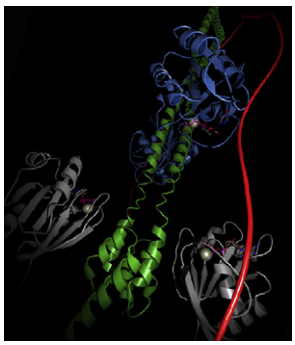


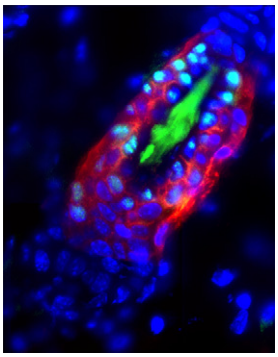
GTPases of the Rab and Arf families participate in regulation of vesicle transport and tethering by recruiting specific effector proteins to the membranes. Here, Burguete et al. show that two of these GTPases, Rab6 and Arl1, cooperate to recruit the putative tether protein, GCC185, to the Golgi, and provide mechanistic insight into the process. They show that Rab6 binding to GCC185 promotes the subsequent binding of Arl1. A structure-derived model for dual GTPase membrane attachment highlights the potential ability of Rab GTPases to reach binding partners at a significant distance from the membrane via their unstructured and membrane-anchored, hypervariable domains.

Unexpected Openings in Chromatin

PAGE 311

The majority of DNA in the human genome is condensed into a complex chromatin structure; however, binding of transcription factors to regulatory sequences requires access to DNA. Boyle, et al. now identify regions of DNaseI hypersensitive sites, or open chromatin, across the human genome using DNaseI treatment and high-throughput sequencing and microarray technologies. Regions that are most sensitive are found at the transcription start sites of actively transcribed genes. However, the majority of open chromatin sites are not at transcription start sites. This open chromatin map delineates active genomic regions that can be further explored for their functional roles.

NFATuated with Stem Cell Quiescence



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Adult stem cells are generally quiescent and produce proliferative progeny during injury and tissue homeostasis. The mechanisms that control cellular quiescence in stem cells are unknown. Horsley et al. have now identified a control mechanism for stem cell activity in the skin. Expression of NFATc1 in bulge stem cells is necessary and sufficient for inducing slow cycling characteristics in keratinocytes. NFATc1 represses *CDK4* expression and acts downstream of BMP signaling to inhibit bulge cell proliferation. The data identify mechanisms for controlling stem cell activity in the skin.